DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Nadine Cohen, Ph.D.
Senior Vice President, Regulatory Affairs
Biogen Idec
14 Cambridge Center
Cambridge, MA 02142

RE: BLA # 103628
AVONEX® (Interferon beta-1a) IM Injection
MA # 374

Dear Dr. Cohen:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed Biogen Idec's (Biogen) webpages, "Long Term Results" and "Multiple Sclerosis Treatments," which are part of a consumer website[1] for AVONEX® (Interferon beta-1a) IM Injection (Avonex). These webpages are misleading because they overstate the efficacy of Avonex, omit material information, and present unsubstantiated superiority claims for the drug. Thus the webpages misbrand Avonex in violation of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), 21 U.S.C. 352(a), (n); 321(n). *See* 21 CFR 202.1(e)(5)(iii); (e)(6)(i), (ii); (e)(7)(i).

Background

Below is the indication and summary of the most serious and most common risks associated with the use of Avonex.[2] According to its FDA-approved product labeling (PI)[3]:

> AVONEX® (Interferon beta-1a) is indicated for the treatment of patients with relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis. Safety and efficacy in patients with chronic progressive multiple sclerosis have not been established.

[1] Avonex webpages, "Long Term Results" and "Multiple Sclerosis Treatments," http://www.avonex.com (last accessed September 7, 2011).
[2] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional pieces cited in this letter.
[3] The version of the PI that was approved when the piece cited in this letter was disseminated and the version referred to in this letter is dated February 2, 2007. However a new version of the PI was approved on February 27, 2012.

Avonex is associated with a number of serious risks. According to its PI, Avonex is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta or any component of the drug, and the lyophilized vial formulation of Avonex is contraindicated in patients with a history of hypersensitivity to albumin (human). There are Warnings in the Avonex PI regarding depression and suicide, anaphylaxis, decreased peripheral blood counts, hepatic injury, and albumin (human). In addition, there are Precautions regarding seizures, cardiomyopathy and congestive heart failure, and autoimmune disorders.

The most commonly reported adverse reactions associated with the use of AVONEX were flu-like and other symptoms occurring within hours to days following an injection. Symptoms can include myalgia, fever, fatigue, headaches, chills, nausea, and vomiting. Some patients experienced paresthesias, hypertonia and myasthenia.

Overstatement of Efficacy

Promotional materials are misleading if they represent or suggest that a drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience.

The "Long Term Results" webpage includes the following claims and presentations (emphasis in original):

- "**Long Term Results**

  AVONEX may help you stay active and able longer

  Your doctor or nurse may use the Expanded Disability Status Scale (EDSS) to measure how you are doing. The scale measures disability progression by looking at various functional areas including your ability to walk. Areas include:

• Brain function • Coordination skills • Bowel and bladder function	• Sensory and motor symptoms • Visual symptoms • Ability to walk

  In a long-term follow up study [a], **8 out of 10** people taking AVONEX had an EDSS score below **3.0 at 10 years**, which means they were still active and able."
- A pictorial representation of the EDSS and the claim, "**80% below EDSS 3.0 at 10 years**."
- "[a] A 10 year follow-up of a 3-year study of people who had a first attack and lesions consistent with MS on their MRIs."

This presentation misleadingly overstates the efficacy of Avonex by implying that the drug will enable 8 out of 10 (80%) patients with relapsing forms of multiple sclerosis to stay active and able for 10 years, when this has not been demonstrated by substantial evidence or substantial clinical experience. The clinical studies included in the PI for Avonex only support the efficacy of the drug for up to **three years** in duration. Specifically, the CLINICAL STUDIES section of the PI states, "Safety and efficacy of treatment with Avonex® beyond 3 years is not known." Furthermore, the study cited on the website is **not** an adequate and well-controlled clinical study because it is a 10-year, open-label, follow-up study; therefore, it does not constitute substantial evidence to support long-term efficacy claims on progression of disability beyond three years. We note that the following statement is included on the "Long Term Results" webpage: "FDA-approved labeling includes up to 3 years of clinical data"; however, this statement does not mitigate the misleading presentation on the webpage.

In addition, this presentation misleadingly overstates the efficacy of Avonex by implying that the drug is effective for each of the individual functional areas of the EDSS that are listed on the webpage. According to the CLINICAL STUDIES section of PI, the efficacy of Avonex in slowing the accumulation of physical disability was demonstrated based on a study of time to progression in disability, measured as an increase in the EDSS total score of at least 1.0 point that was sustained for at least 6 months. The study did **not** evaluate the impact of treatment with Avonex on each individual functional area included in the EDSS, such as brain function, coordination skills, bowel and bladder function, sensory and motor symptoms, visual symptoms or the ability to walk. FDA is not aware of substantial evidence or substantial clinical experience to support the implication that treatment with Avonex will allow patients to maintain their level of function in each of these individual areas of the EDSS. If you have data to support such claims, please submit them to FDA for review.

Omission of Material Information/Unsubstantiated Superiority Presentation

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. Promotional materials are also misleading if they contain a comparison that represents or suggests that a drug is safer or more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience.

The "Multiple Sclerosis Treatments" webpage presents the following claims and presentations (emphasis in original):

- "When you are first diagnosed with multiple sclerosis, you may wonder which therapy is the best one for you. . . .

  Not all relapsing MS treatments are the same

  AVONEX is the only once-a-week multiple sclerosis treatment proven to slow

physical disability, reduce flare-ups, and work after the first attack."

- A chart comparing Avonex® (interferon beta-1a), Copaxone® (glatiramer acetate), Rebif® (interferon beta-1a), and Betaseron®/Extavia® (interferon beta-1b) on several attributes, such as the year of FDA approval, whether or not the drug slows physical disability progression, reduces flare-ups, or is effective after the first attack, the method of administration, the number of doses per year, and whether or not the drug is available as a prefilled syringe.

The totality of this presentation misleadingly implies that Avonex is superior to Copaxone, Rebif, Betaseron, and Extavia solely based on the select attributes presented. The chart shows that Avonex was approved in 1996, slows physical disability, reduces flare-ups, works after the first attack, is associated with fewer doses per year, and is available as an intramuscular injection in a prefilled syringe. The chart also presents information about these attributes for Copaxone, Rebif, Betaseron and Extavia. We note that the information included in the chart is consistent with the PI for each drug product. However, by failing to present information about other attributes associated with these products, the webpage misleadingly implies that Avonex is superior to the other drugs. For example, this presentation omits material information about Avonex, such as information about contraindications, serious warnings and precautions, and laboratory test monitoring, which is highly relevant to any decision about whether to prescribe or take Avonex or another drug for relapsing forms of multiple sclerosis. We acknowledge that some of the safety information for Avonex is presented in the Important Safety Information section at the bottom of the webpage. However, the inclusion of such information in small font at the bottom of the webpage does not mitigate the misleading implication that Avonex is superior to Copaxone, Rebif, Betaseron, and Extavia. FDA is not aware of substantial evidence or substantial clinical experience demonstrating that Avonex is safer, more effective, or otherwise superior to Copaxone, Rebif, Betaseron or Extavia. If you have data to support such claims, please submit them to FDA for review.

Conclusion and Requested Action

For the reasons discussed above, the webpage misbrands Avonex in violation of the FD&C Act, 21 U.S.C. 352(a), (n); 321(n). *See* 21 CFR 202.1(e)(5)(iii); (e)(6)(i), (ii); (e)(7)(i).

OPDP requests that Biogen immediately cease the dissemination of violative promotional materials for Avonex such as those described above. Please submit a written response to this letter on or before March 28, 2012, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Avonex that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Direct-to-Consumer Promotion, 5901-B Ammendale Road, Beltsville,**

Maryland 20705-1266 or by facsimile at (301) 847-8444. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Promotion (DPP) and the Division of Direct-to-Consumer Promotion (DDTCP). To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to the MA # 374 in addition to the BLA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Avonex comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Quynh-Van Tran, PharmD, BCPP
Regulatory Review Officer
Division of Professional Promotion
Office of Prescription Drug Promotion

Amy Toscano, PharmD, CPA
Team Leader
Division of Direct-to-Consumer Promotion
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/s/

QUYNH-VAN TRAN
03/14/2012

AMY TOSCANO
03/14/2012